

### **Remarks**

Reconsideration of the application is respectfully requested in view of the foregoing amendments and following remarks. No claims are added or canceled. Therefore, upon entry of this amendment, claims 1, 2, 6, 8-17 and 36-38 will remain pending in the application.

Claims 1, 2, 6, 8, 9, 16, and 37 are amended herein. Support for the claim amendments can be found throughout the specification, for example:

Claim 1: Claim 1 and page 26, lines 26-33.

Claim 2: Claim 2 and page 23, lines 30-32.

Claim 6: Claim 6 and page 26, lines 26-33.

Claim 8: Page 26, lines 26-33.

Claim 9: Page 26, lines 31-33.

Claim 16: Page 12, lines 37-38; page 14, lines 5-6.

Claim 37: Claim 37 and page 26, lines 26-33.

Applicants thank the Examiner for withdrawing many of the previous rejections. Applicants also thank the Examiner for considering the Information Disclosure Statement submitted on April 2, 2007.

### ***Telephone Interview***

Applicants thank Examiners Spector and Shafer for the courtesy of a telephone interview with their representatives, Sheree Lynn Rybak and Susan W. Graf, on November 6, 2007. During the telephone interview, the rejections under 35 U.S.C. §§ 102 and 112 were discussed. Examiners Spector and Shafer stated that the rejection under § 102(b) will be withdrawn. Potential claim amendments were discussed to address the § 112 rejections. Applicants believe that this amendment addresses the concerns that were discussed regarding the § 112 rejections.

***Claim Rejections Under 35 U.S.C. § 112, Second Paragraph***

The Action rejects claims 1, 2, 6, 8-17, and 36-38 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants request reconsideration in light of the amendments herein.

Claims 1, 2, 6, and 37 are rejected as vague and indefinite in identifying the polypeptide of interest as a mutation of a “polypeptide sequence of GenBank Accession No. Z30425 (SEQ ID NO: 18).” Claims 1, 2, 6, and 37 are hereby amended to remove the Genbank Accession number and recite a “polypeptide sequence of SEQ ID NO: 18.” Therefore, Applicants request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Claims 1 and 37 are rejected as vague and indefinite in reciting a wild type receptor comprising one or more mutations. Claims 1 and 37 are hereby amended to remove the reference to a “wild type” receptor, therefore Applicants request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Claims 1 and 37 are further rejected as vague and indefinite for reciting “one or more mutations” without specifying an upper limit. Claims 1, 6, 8, 9, and 37 are hereby amended to recite “one to ten mutations.” Support for this amendment is found on page 26, lines 26-33, which describes amino acid substitutions as being typically “1, 2, 3, 4, 5, 10 or more substitutions.” In light of this amendment, Applicants request withdrawal of this rejection.

Claim 2 is rejected as vague and indefinite for reciting that the “one or more mutations” correspond to Leu342 and Leu343. Claim 2 is hereby amended to recite “wherein the mutations comprise” positions Leu342 and Leu343. Applicants request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Claim 16 is rejected as vague and indefinite in reciting a “CAR-responsive steroid.” Applicants contend that this term is clearly defined in the specification, for example at page 12, lines 37-38 (“a CAR-responsive steroid, such as estrogen, is one that can activate CAR and result in steroid metabolizing or degrading activity”). However, solely to expedite prosecution, claim 16 is hereby amended to recite a “CAR-activating steroid.” Claim 16 is further amended to recite a “CAR-

activating xenochemical” to clarify that the kit comprises a CAR-activating steroid and/or a CAR-activating xenochemical. Support for these amendments is found at least at page 12, lines 37-38 and page 14, lines 5-6. In light of this amendment, Applicants request withdrawal of this rejection.

Claim 1 is rejected as vague and indefinite for reciting “less constitutively active.” The definition cited by the Office action on page 5, first paragraph is a definition of a *non*-CAR found in the specification, not a definition of “less constitutively active.” The specification defines a variant having decreased (or less) constitutive activity on page 25, lines 21-24 as one having “at least 20%, at least 50%, at least 80%, at least 90%, at least 95%, or at least 98% of constitutive activity” as determined by the method described in Example 1. One of ordinary skill in the art would understand this to mean that a less constitutively active receptor is one that has decreased activity compared to a constitutively active receptor under the same assay conditions. Applicants request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Claim 9 is rejected as vague and indefinite for reciting “substantially decrease the non-constitutive activity.” Claim 9 was amended in the amendment entered on April 2, 2007 to remove the allegedly indefinite language “substantially decrease the non-constitutive activity.” Claim 9 as previously presented recites “substitutions which do not substantially alter the constitutive activity.” Therefore, Applicants respectfully request that the rejection on this ground be withdrawn.

### ***Claim Rejections Under 35 U.S.C. § 112, First Paragraph***

#### **Enablement**

Claims 1, 9-17, and 36 are rejected under 35 U.S.C. § 112, first paragraph as lacking enablement. The Office action alleges that the specification, while being enabling for an isolated polypeptide wherein the polypeptide comprises mutations at position Leu 342 or Leu 343 in a human polypeptide of SEQ ID NO:18, does not reasonably provide enablement for an isolated polypeptide wherein the amino acid sequence of the polypeptide comprises one or more mutations at any residue position in SEQ ID NO:18. The Office action contends that undue experimentation would be required for one of skill in the art to make and/or use the claimed invention. Applicants traverse.

The Office action contends that there is a lack of guidance in the specification regarding which

residues other than 342 and 343 of SEQ ID NO: 18 are to be mutated and an absence of working examples directed to this matter. The specification contains at least two additional examples of mutations which render mCAR substantially non-constitutively active: Thr176 to Val 176 and Glu 355 to Ala355 (page 15, lines 16-19). Example 6 (page 23) provides an example of the decreased constitutive activity of a mCAR T176 mutation. The specification further points out that one of skill in the art would understand that corresponding mutations may be made in CARs from other species (page 15, lines 22-23; page 23, lines 4-6). Thus, there is guidance regarding which residues can be mutated and there are working examples.

The Office action further alleges that the claims are not enabled “due to the large quantity of experimentation necessary to generate the infinite number of derivatives . . . and screen same for activity.” Applicants respectfully disagree. The claims as amended are drawn to hCAR comprising *one to ten* mutations. Any necessary experimentation would be routine. The specification extensively teaches how one would generate a CAR comprising one to ten mutations (page 13, lines 17-37; Example 9, pages 25-26) and methods of determining activation and responsiveness of the resulting variants in a cell-based transfection assay (Example 1, page 19, lines 4-19). Therefore, all that remains to be done is to follow the teaching of the specification.

Based on the foregoing discussion, Applicants request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

## **Written Description**

Claims 1, 9-17 and 36 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Applicants traverse the rejection and request reconsideration in light of the amendment of claims 1 and 9 and the following discussion.

The Office action alleges that the claims are drawn to a genus of polypeptides of SEQ ID NO: 18 comprising one or more mutations, with no upper limit. Applicants herein amend claims 1 and 9 to recite a CAR comprising “one to ten mutations,” providing an upper limit on the number of mutations.

Further, the Office action contends that only two species of the claimed genus are disclosed *i.e.*, polypeptides comprising mutations at position Leu 342 or Leu343. However, at least four species of

the claimed genus are disclosed – “one or more mutations . . . *corresponding to* murine CAR (mCAR) position Thr176, mCAR position Leu352, mCAR position Leu353 [and] mCAR position Glu355” (page 2, lines 19-21) A nucleic acid or amino acid of one sequence is defined by the specification as corresponding to a nucleic acid or amino acid of another sequence if “when the sequences are optimally aligned . . . the nucleic acids or amino acids align with one another” (page 8, lines 1-4). As an example, the specification indicates that T176 of mouse CAR corresponds to T166 of human CAR. Based on this description, one of skill in the art would recognize that Applicants had possession of the claimed invention.

Factors to be considered in determining adequate written description include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, or a combination thereof. The specification discloses the structure of the polypeptide (SEQ ID NO: 18) and functional characteristics of variants comprising one to ten mutations, *i.e.* that the mutation(s) renders the polypeptide less constitutively active than the CAR polypeptide of SEQ ID NO: 18. Support is found throughout the specification, and at least at page 6, lines 24-26; page 15, lines 1-5; and page 25, lines 21-24

The disclosure of a representative number of species, in addition to a description of structural and functional characteristics, demonstrates that Applicants had possession of the claimed invention at the time the application was filed. Therefore Applicants request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

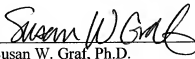
**Conclusion**

As the present amendment places the application in condition for allowance, Applicants request that it be entered. If any matters remain to be discussed before a Notice of Allowance is issued, the Examiner is respectfully requested to contact the undersigned for a telephone interview at the telephone number listed below.

Respectfully submitted,

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